

## LETTERS TO THE EDITOR

### CYANAMIDE OR DISULFIRAM IN THE TREATMENT OF ADOLESCENT ALCOHOL MISUSERS?

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The Randomised Controlled Trial by Niederhofer *et al.* (2003) describing the successful use of cyanamide in a group of alcohol-misusing adolescents, is further and convincing evidence of the effectiveness of deterrent or antagonist medication in the management of some types of substance misuse. However, despite the obvious similarities in mode of action between cyanamide and disulfiram, I am puzzled that the above authors made absolutely no mention of the use of disulfiram in treatment.

Ironically, their only reference to disulfiram is to a paper which compares its hepatotoxicity with that of cyanamide. Yet the literature strongly suggests that, whereas cyanamide causes histological changes in many patients, disulfiram causes only rare and idiosyncratic hepatotoxicity, which is commoner in women and is probably due to nickel sensitivity from costume jewellery (Brewer and Hardt, 1999).

Although Niederhofer *et al.* (2003) did not specifically mention it, their paper gives the impression that the patients in this study were subjected to unusually high levels of supervision and control and that the treatment programme did not ignore the very important issue of compliance with medication. This necessarily involves a degree of supervision. Perhaps the main reason for the relatively infrequent use of deterrent medication is the failure of many reviewers of the literature to note the crucial distinction between those studies in which the administration of medication was supervised, which are almost universally positive at statistically significant levels, and those studies in which medication was unsupervised, which almost universally show no more effectiveness than placebo medication (Brewer *et al.*, 2000; Brewer and StreeL, 2003). Niederhofer *et al.* (2003) rightly draw attention to the probable superiority of deterrent medications to drugs, such as naltrexone and acamprosate, in alcoholism treatment. They

could have strengthened their argument by mentioning studies comparing disulfiram with naltrexone or acamprosate which support that view (see, e.g. Carroll *et al.*, 1993)

Finally, it would be interesting to know why Niederhofer *et al.* (2003) chose a drug which needs to be given three times daily when they could have used disulfiram, which only needs to be given once daily or even thrice weekly. Nevertheless, I congratulate them on a well-planned study in a group of patients who are often resistant to treatment. The above authors stated that 'alcoholism in adolescence is very likely to become an important problem within the next few decades'. Perhaps the youth of Salzburg are unusually docile: many of us in Britain would say that the problem is already important and has a significant and unpleasant impact on the life of our cities.

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#### REPLY

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It was the purpose of our double-blind, placebo-controlled study to verify the efficacy of cyanamide in the treatment of adolescent alcohol abusers (Niederhofer *et al.*, 2003).

Cyanamide is registered for the treatment of alcohol misusers; we therefore thought it would be appropriate to ascertain its efficacy, and in particular its safety, in adolescents. Disulfiram

has been reported to be effective in treating this type of patient, as suggested by Brewer (2003), whereas Fuller and Roth (1979) found disulfiram to be of limited value only. Besson *et al.* (1998) pointed out that disulfiram may improve abstinence rates from 43 to 73% when combined with anti-craving medication (acamprostate). Severe side-effects, such as disulfiram hepatitis, were observed (Wright *et al.*, 1988) in patients taking it as a deterrent medication. As far as we know, there are no systematic studies reporting the rates of adverse side-effects of these drugs, in particular disulfiram hepatitis, cyanamide-induced pancytopenia (for adults see e.g. Yerro *et al.*, 2000) or histological changes of the liver in adolescents (for adults see e.g. Yokoyama *et al.*, 1995). Moreover, the rate of pre-existing liver damage, related also to the duration of alcohol dependency, seems to be lower in adolescents than in adults. Finally, in the UK, alcoholism is more often combined with the intake of other illegal drugs than it is in other European countries. For this reason, the risk of liver damage seems to be of little importance in our population, and thus we decided to check cyanamide for its efficacy.

Feuerlein (1986) reported a higher relapse rate in adolescents than occurs in adults. This may lead to a higher probability that adolescents might continue or restart drinking while taking disulfiram or cyanamide. For this reason, we think that the use of substances such as disulfiram, which may cause severe adverse effects such as hepatitis, especially if combined with alcohol intake (Fraser, 1997), should be avoided. Cyanamide is reported to have fewer severe side-effects when combined with alcohol intake (Aragon *et al.*, 1993), although its administration is not convenient as it has to be given three times daily, whereas disulfiram needs to be given only once a day.

Because there is a possibility of potential liver damage due to cyanamide in adolescents, the participants of our study were followed-up closely. This may have led to the significance of our results. Other studies, however, reported the superiority of deterrent medications to drugs such as naltrexone or acamprostate

(Carroll *et al.*, 1993) and because of this we did not compare cyanamide with these substances. We merely studied a drug which is more effective than naltrexone or acamprostate, for example, and also safer than disulfiram when combined with alcohol.

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## REPLY TO THE COMMENTARY BY KARI POIKOLAINEN ON EVALUATION OF THE EFFECT OF TREATMENT OF ALCOHOL AND DRUG PROBLEMS BY THE SWEDISH COUNCIL ON TECHNOLOGY ASSESSMENT IN HEALTH CARE (SBU)

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We appreciate the careful reading and evaluation of the Swedish Council on Technology Assessment in Health Care (SBU, 2001) report by Dr Poikolainen (SBU, 2002). Poikolainen discusses several important issues, not only related to the

report but also to systematic reviews in general. First, we shall comment on the SBU methodology.

## SBU METHODOLOGY

It is important to stress that the methodology applied is basically a series of systematic reviews of the available literature. The use of meta-analytical procedures depends on

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the character of the studies on the different topics. In most previous SBU reports meta-analytical techniques have not been applied. In our opinion, the development of meta-analytical methodology and the availability of effective software for performing meta-analytical calculations have made this technique simple and more applicable for systematic literature reviews. The number of meta-analytical reviews in most scientific fields, including alcohol and drug treatments, have also rapidly increased in recent years.

It is also important to stress that the procedure after the completion of the reviews, including a first draft of Council's executive conclusions, and leading to the final report, is rather extensive. It includes reviews by external experts and by the SBU's Executive Board and Scientific Advisory Board, where the evidence was carefully evaluated. The process from final review to publication took more than a year.

We should now like to acknowledge some shortcomings of the Swedish version of the SBU report and then to discuss a few of the issues raised by Poikolainen.

#### SHORTCOMINGS OF THE SWEDISH VERSION OF THE SBU REPORT

##### *Incorrect presentation of effect sizes*

Unfortunately, in some of the meta-analyses in the chapter on psychosocial treatments and pharmacological treatments of alcohol dependence, and pharmacological treatments of drug dependence, log odds, instead of  $d$  with Hedge's correction, have been presented as the effect size. This increases the effect size, but does not influence levels of significance. This has been corrected in the English version, and a correction will also be made available in Swedish.

##### *Meta-analytical procedures did not include calculations of homogeneity/heterogeneity and search for moderator effects*

In the English version we have recalculated most of the meta-analyses using the software program of Borenstein and Rothstein (1998). Tests for heterogeneity have been performed and, if positive, a search for moderator effects has been done. If no moderator has been identified, the results both of a fixed and of a random model are presented. With these changes we regard the meta-analyses being up-to-date concerning methodology.

In his commentary, Poikolainen states as if it were a matter of fact that only studies with similar patient groups should be included in a meta-analysis. However, this is open to debate. Obviously, studies must have some common elements if it is to be meaningful to pool them. If, on the other hand, studies are too similar, one loses the opportunity for generalizability that Poikolainen demands. So using a random-effects model, when statistical heterogeneity is detected or, in many cases, even when the test for heterogeneity is not significant, it is possible to pool rather different studies. If level of severity, dose, intensity, treatment duration or other moderator variables do not make too great a difference, generalizability is present. We could have further developed this type of analysis if time had permitted. Search for moderator effects using meta-regression is, however, a retrospective procedure with considerable risk for spurious relationships, especially when few studies are available in the meta-analysis.

##### *Lack of chapter on methodology*

It would be an advantage to have a general chapter on methodology. In the Swedish version methodological aspects are presented in the individual chapters. The main outcome measures have been related to misuse: in alcohol dependence the abstinence rate and in some cases the rate of not returning to heavy drinking, and in drug dependence both misuse and retention. Other outcome measures have generally not been included in the analyses, with the exception of the studies on psychiatric comorbidity in which psychiatric outcome methods have been included. A major reason for not using more functional outcomes is the fact that most primary studies do not measure them. In the English publication, a general methodology chapter has been added.

##### *Problems with data abstracting*

We acknowledge problems with data abstracting. We have carefully reviewed most of the critical studies again and corrected obvious faults. Many decisions in the data abstracting, however, are not clear-cut. A statistician has been consulted in several of the more complicated cases. Data abstracting has been considerably improved in the English version. However, the abstracting procedure is very costly and time-consuming and could be further improved (e.g. by contacting the authors of the papers). The improvements have so far not influenced the main conclusions.

#### ADDITIONAL ISSUES

##### *D-statistics and dichotomous data*

We acknowledge problems with  $d$ -statistics and dichotomous data, which have been discussed extensively in the literature, as Poikolainen points out. It is, however, an acceptable procedure from a statistical point of view. Effects will always be influenced by the baseline risk (result in the control group), regardless of the outcome being analysed dichotomously or continuously.

This methodology has been successfully used by Moyer *et al.* (2002) concerning secondary prevention and psychosocial treatment in alcohol problems. The success of their attempt was acknowledged by the editorial comments on the paper (Heather, 2002). They used a similar approach as the one we use in the English publication. Most of their analyses were homogenous from a statistical point of view.

##### *Brief intervention*

With the publication of the excellent meta-analysis by Moyer *et al.* (2002) in *Addiction*, the lack of a meta-analysis in the SBU report can certainly be criticised. However, the qualitative conclusion is still valid. The suggested contradiction in the executive summary is mainly caused by careless reading. The summary states that we have no strong scientific support for describing a certain level of alcohol intake as safe. In practice, the summary continues, researchers are in reasonable agreement. It is this somewhat pragmatic agreement that makes the foundation for the calculations of the number needed to treat (NNT).

##### *Project MATCH study*

It is correct that in the Project MATCH Research Group (1997) study, the authors conclude that there are no 'clinical'

significant differences between the different therapies described in the article. However, in the same article they report some significant differences between the therapies according to the primary efficacy variables as well as in some of the secondary variables.

#### Review verdict

As it is the scientific community and not the 'prosecutor', Poikolainen, that passes the verdict, we rest assured that our main conclusions are strongly supported by the studies reviewed and that, although Poikolainen has made several helpful comments, the statement that the main findings are not to be trusted is unfounded and not supported by the review presented.

### CONCLUSIONS

In conclusion, the ambitions of the SBU report, to include the entire literature concerning treatment of alcohol and drug dependence, has some limitations concerning precision and sophistication in methodology compared with smaller reviews and analyses. However, using similar techniques in data abstracting with one statistician advising all authors, comparability between the different chapters and their conclusions probably could be assumed to be better than in a total body of smaller

independent analyses. We acknowledge several weaknesses in the Swedish report, which we have corrected in the English version. No changes in analysis and data abstractions, however, have had any influence on the initial findings.

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### REPLY

## THE SBU EVALUATION OF THE EFFECT OF TREATMENT OF ALCOHOL AND DRUG PROBLEMS

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I am happy that the authors (Berglund and Thelander, 2003) have found several of my comments (Poikolainen, 2002) helpful and have improved their data and methods. It is the quality of those data and methods that determines the credibility of the findings and conclusions. Careful reading of the critical reviews on the SBU (2001) report should suggest further improvements.

Encouraged by the authors' constructive response to scientific criticism, I recommend some new improvements to be incorporated into the next edition. (1) Please make available all data abstracted from the original articles that were used in the calculations, at least in the internet edition. This would help possible future meta-analyses. (2) Please define the level of alcohol intake used in the calculations of the number needed to treat (NNT). (3) Also, whenever possible, please present the effect sizes based on NNT, odds ratios or mean changes. It is misleading to compare the effects of various treatments, an important aim of your project, with *d*-statistic. The *d*-statistic varies markedly for reasons other than the treatment effect — from 1.0 to 2.3 in cases where NNT is always

10. To have unbiased estimates on the efficiency of treatments is also crucial to determine that there is real clinical significance, not only statistical significance. Statistical significance is easy to reach in large meta-analyses, but may be clinically irrelevant.

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